Table 1

Quantitative Measurements in 145 Patients with Stage I Adenocarcinoma

Parameter	All Patients	Patients with Pure GGN	Patients with Part-Solid GGN	Patients with Solid Tumor
Visual analysis				
Longest diameter of tumor (mm)	15.7 ± 4.8 (7.0–31.0)	11.2 ± 2.7 (7.0–14.9)	15.9 ± 4.6 (7.2–31.0)	16.9 ± 5.1 (7.0–31.0)
Longest diameter of solid component (mm)	9.6 ± 7.0 (0.0–31.0)	0.0 ± 0.0 (0.0–0.0)	7.5 ± 4.7 (1.0–21.0)	16.9 ± 5.1 (7.0–31.0)
Solid proportion (%)	58.3 ± 37.1 (0.0–100.0)	0.0 ± 0.0 (0.0–0.0)	47.2 ± 26.5 (11.4–95.0)	100.0 ± 0.0 (100.0–100.0)
Computer analysis				
Tumor volume (cm^3)	2.46 ± 2.87 (0.03–16.97)	0.64 ± 0.54 (0.03–1.62)	1.92 ± 2.23 (0.05–15.60)	4.01 ± 3.58 (0.45–16.97)
Solid volume (cm^3)	1.47 ± 2.18 (0.00–14.28)	0.00 ± 0.02 (0.00–0.12)	0.75 ± 0.82 (0.003–4.09)	3.22 ± 3.00 (0.35–14.28)
Solid volume (%)	49.1 ± 28.2 (0.00–90.40)	0.21 ± 0.5 (0.00–1.90)	40.9 ± 19.9 (6.30–71.50)	78.7 ± 5.0 (71.60–90.40)

Note.—Data are mean ± standard deviation. Data in parentheses are range. For group classification, there were 145 patients total, 15 with pure GGN, 83 with part-solid GGN, and 47 with solid tumor. For visual analysis, there were 145 patients total, 15 with pure GGN, 86 with part-solid GGN, and 44 with solid tumor.

Statistical Analysis

We evaluated the value of eight features of CT (visual classification, software classification, longest diameter of solid component, longest diameter of total tumor, solid proportion, total tumor volume, solid volume, and percentage of solid volume) to examine associations with three prognostic factors (lymphatic invasion, vascular invasion, and pleural invasion) and two outcome measures (overall survival and disease-free survival). All statistical analyses were performed by using commercially available software (MedCalc version 8.0.0.1; Frank Schoonjans, Mariakerke, Belgium). Agreement between visual and software classification of nodule subgroups was evaluated by using the κ statistic, and it was classified as poor (κ = 0.00–0.20), fair (κ = 0.21–0.40), moderate (κ = 0.41–0.60), good (κ = 0.61–0.80), or excellent (κ = 0.81–1.00) (21). For each CT feature, the cutoff value that yielded the largest difference in numbers of patients with and without recurrence and death was determined by using the empirical receiver operating characteristic method. Receiver operating characteristic analyses were all univariate. The optimal thresholds were determined for each variable separately. Subsequently, associations between prognostic factors and each binary group designated by the cutoff value for the eight CT features were evaluated by using univariate logistic regression analysis. Similarly, associations between outcome measures and each binary group were evaluated by using univariate Cox proportional hazards regression analysis. Significant parameters identified by univariate analysis were included in the multiple logistic regression and Cox proportional hazards regression models (stepwise method; *P* value of .05 or less was used for entry into the model and *P* value greater than .1 was selected for removal), respectively. The 123 patients (85.0%) with no observed failure events in the present study were considered censored for the two outcome measures in the Cox proportional hazards regression model. Survival curves were generated by the Kaplan-Meier method, with comparisons performed by using the log-rank test. A *P* value of less than .05 indicated statistical significance.

Results

Visual and Computer Analyses

Results of all 145 patients are summarized in Table 1. Classification of nodules (per two radiologists) into pure GGN, part-solid GGN, and solid subtypes showed excellent agreement (κ = 0.90). There was excellent agreement (κ = 0.81) between visual and computer classification of nodule subgroups with disagreements on only five nodules.

Distribution of pure GGN was peripheral (*n* = 12), middle (*n* = 2), and juxtapleural (*n* = 1); distribution of part-solid GGN and solid nodules was peripheral (*n* = 72), middle (*n* = 8), and juxtapleural (*n* = 50). Mean measured longest diameter of solid component and total tumor were 9.6 mm ± 7.0 (range, 0–31.0 mm) and 15.7 mm ± 4.8 (range, 7.0–31.0 mm), respectively. Calculated solid proportion of nodules was 58.3%–37.1% (range, 0%–100%). Total tumor volume, solid volume, and percentage solid volume were 2.46 cm^3 ± 2.87 (range, 0.033–16.97 cm^3), 1.47 cm^3 ± 2.18 (range, 0–14.28 cm^3), and 49.1% ± 28.2 (range, 0%–90.4%), respectively.

Pathologic Analysis

There were identified lymphatic invasion in 17 cases, pleural invasion in 13 cases, and no cases of vascular invasion. There were 118 patients staged as pT1a, 14 patients staged as pT1b, and 13 patients staged as pT2. No patients were found to have lymph node metastases. According to pathologic analysis, there were 132 patients staged as Ia and 13 patients staged as Ib.

Relationship with Prognostic Factors

On the basis of receiver operating characteristic analysis, both visually and computer-classified subgroups were re-sorted into pure GGN and solid (part-solid GGN and solid) divisions. Cutoff values for the six CT features were as follows: longest diameter of solid component, 9.9 mm; longest tumor diameter, 18 mm; solid proportion, 78%; total tumor volume,

Table 2

Relationship of CT Features with Prognostic Factors

	Lymphatic Invasion ($n = 145$)			Pleural Invasion ($n = 51$)		
Logistic Regression Analysis	No. of Tumors	Odds Ratio	*P* Value	No. of Tumors	Odds Ratio	*P* Value
Univariate analysis						
Visual classification						
Pure GGN	15	1.96 (0.24, 15.97)	.49	1	ND*	ND*
Solid	130	...	...	50	ND*	ND*
Software classification						
Pure GGN	15	1.96 (0.24, 15.97)	.49	0	ND*	ND*
Solid	130	...	...	51	ND*	ND*
Longest diameter of tumor						
<18 mm	94	1.01 (0.35, 2.90)	.99	27	0.95 (0.27, 3.37)	.94
≥18 mm	51	...	...	24	...	...
Longest diameter of solid component						
<9.9 mm	81	2.17 (0.67, 6.99)	.19	21	3.00 (0.71, 12.65)	.13
≥9.9 mm	64	...	...	30	...	...
Solid proportion						
<78%	90	2.04 (0.65, 6.43)	.22	24	4.12 (0.98, 17.38)	.05
≥78%	55	...	...	27	...	...
Total tumor volume						
<1.9 cm^3	84	0.96 (0.34, 2.68)	.94	21	1.16 (0.32, 4.23)	.81
≥1.9 cm^3	61	...	...	30	...	...
Solid volume						
<1.5 cm^3	101	1.29 (0.45, 3.75)	.64	26	1.30 (0.37, 4.58)	.69
≥1.5 cm^3	44	...	...	25	...	...
Percentage of solid volume						
<63%	88	2.46 (0.88, 6.90)	.08	23	6.03 (1.58, 22.98)	.01
≥63%	57	...	...	28	...	...
Multiple analysis (by stepwise method)						
Percentage of solid volume						
<63%	88	ND	ND	23	6.03 (1.58, 22.98)	.01
≥63%	57	ND	ND	28	...	...

Note.—Data in parentheses are 95% confidence intervals. *P* values less than .05 indicated statistical significance. ND = no data.

* Statistical analysis for association with pleural invasion could not be performed because of a small number of juxtapleural nodules in GGN division.

1.9 cm^3; solid volume, 1.5 cm^3; and solid volume, 63%.

Results for association of eight CT features with two prognostic factors are summarized in Table 2. Statistical analysis was performed to examine associations with lymphatic invasion in 145 cases and pleural invasion in 51 cases; none of the resected tumors were found by using pathologic examination to have vascular invasion. Statistical analysis for examining the association with pleural invasion was performed only for those tumors that were juxtapleural in location. None of the eight CT features were found to be of use in examination of presence of lymphatic invasion. Univariate and multiple logistic regression analyses revealed that percentage of solid volume of 63% or greater was of significant use in examination of presence of pleural invasion (odds ratio, 6.03 [95% confidence interval: 1.58, 22.98]; $P = .01$).

Relationship with Recurrence and Survival

During a 7-year follow-up period, 22 patients experienced disease recurrence, and there were seven associated cancer-related deaths. All cases of recurrence and death occurred in patients with tumors classified as part-solid GGN ($n = 6$) or solid ($n = 16$); none occurred in patients with tumors classified as GGN.

Results for relationship of eight CT features with disease-free survival and overall survival are summarized in Table 3. Multiple analyses showed that percentage of solid volume of 63% or greater was a significant indicator for lower disease-free survival ($P < .001$). Both univariate and multiple analyses showed that solid volume of 1.5 cm^3 or greater and three-dimensional percentage of solid of 63% or greater were significant ($P < .05$) indicators for lower overall survival. Figures 4 and 5 show the lower disease-free and

Table 3

Association of CT Features with Survival

		Disease-free Survival		Overall Survival	
Cox Proportional Hazards Regression Analysis	No. of Tumors	Hazard Ratio	*P* Value	Hazard Ratio	*P* Value
Univariate analysis					
Visual classification					
Pure GGN	15	310644 (0.00, 3.48×10^{198})	.097	113504 (0.00, 5.23×10^{198})	.375
Solid	130	...	...	...	...
Software classification					
Pure GGN	15	310644 (0.00, 3.48×10^{198})	.097	113504 (0.00, 5.23×10^{198})	.375
Solid	130	...	...	...	...
Longest diameter of tumor					
<18 mm	94	2.89 (1.19, 6.98)	.012	2.65 (0.57, 12.22)	.207
≥18 mm	51	...	...	...	...
Longest diameter of solid component					
<9.9 mm	81	9.23 (2.74, 31.02)	<.001	7.93 (0.96, 65.19)	.055
≥9.9 mm	64	...	...	...	...
Solid proportion					
<78%	90	8.12 (2.76, 23.87)	<.001	4.32 (0.84, 22.08)	.080
≥78%	55	...	...	...	...
Total tumor volume					
<1.9 cm^3	84	4.57 (1.96, 11.43)	.001	3.81 (0.84, 12.31)	.086
≥1.9 cm^3	61	...	...	...	...
Solid volume					
<1.5 cm^3	101	7.17 (2.79, 18.35)	<.001	5.90 (1.17, 29.80)	.016
≥1.5 cm^3	44	...	...	...	...
Percentage of solid volume					
<63%	88	8.18 (2.80, 18.35)	<.001	9.58 (2.09, 43.91)	.01
≥63%	57	...	...	...	...
Multiple analysis (by stepwise method)					
Solid volume					
<1.5 cm^3	101	...	...	5.92 (1.17, 30.33)	.034
≥1.5 cm^3	44	...	...	...	...
Percentage of solid volume					
<63%	88	18.45 (4.34, 78.49)	<.001	9.60 (1.17, 78.91)	.036
≥63%	57	...	...	...	...

Note.—Data in parentheses are 95% confidence intervals. *P* values less than .05 indicate statistical significance.

overall survival for patients with solid volume of 1.5 cm^3 or greater (7-year disease-free survival and overall survival rates, 58.6% and 85.1%, respectively) and percentage of solid volume of 63% or greater (7-year disease-free survival and overall survival rates, 60.1% and 86.3%, respectively) compared with patients with solid volume less than 1.5 cm^3 (7-year disease-free survival and overall survival rates, 92.4% and 98.0%, respectively; $P \leq .015$) and percentage of solid volume of less than 63% (7-year disease-free survival and overall survival rates, 96.3% and 98.9%, respectively; $P \leq .01$).

Table 4 shows quantitative measurements, types of resection performed, and sites of recurrence in 22 patients with recurrence and death. Of the eight smallest tumors that were less than 15.5 mm in longest diameter, six tumors (75%) had solid volume of less than 1.5 cm^3 and one (13%) had percent solid volume of less than 63%. A 27-mm part-solid tumor that resulted in patient death had multiple foci of solid components with measured solid volume of 2.77 cm^3 and percentage of solid volume of 29.8% (Fig 6). Ten patients with recurrent disease presented with a solitary lung metastasis that (based upon either biopsy or resection findings) was confirmed to be adenocarcinoma. Only one nodule recurred in the primary tumor lobe of a patient who had undergone segmentectomy; the remaining nine nodules recurred in a nonprimary tumor lobe and were clinically judged to more likely represent metastatic disease than metachronous primaries based on temporal evolution as documented on postoperative surveillance imaging studies.

Figure 4

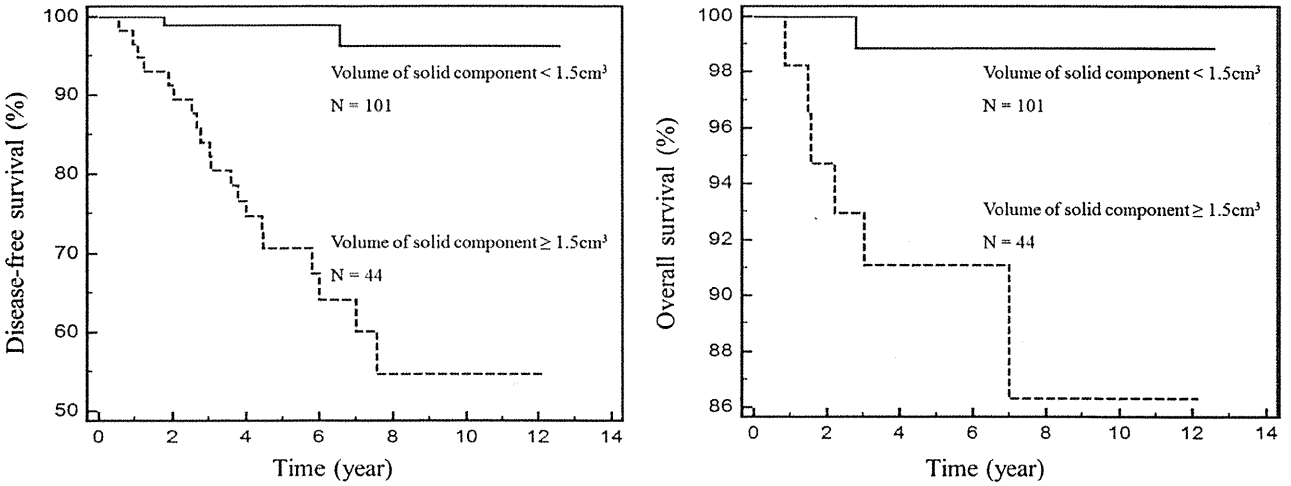

Figure 4: Kaplan-Meier survival curves show that patients with solid tumor volume of 1.5 cm^3 or greater had a significantly lower probability of **(a)** disease-free ($P < .001$) and **(b)** overall survival ($P = .015$) than patients with solid tumor volume less than 1.5 cm^3.

Figure 5

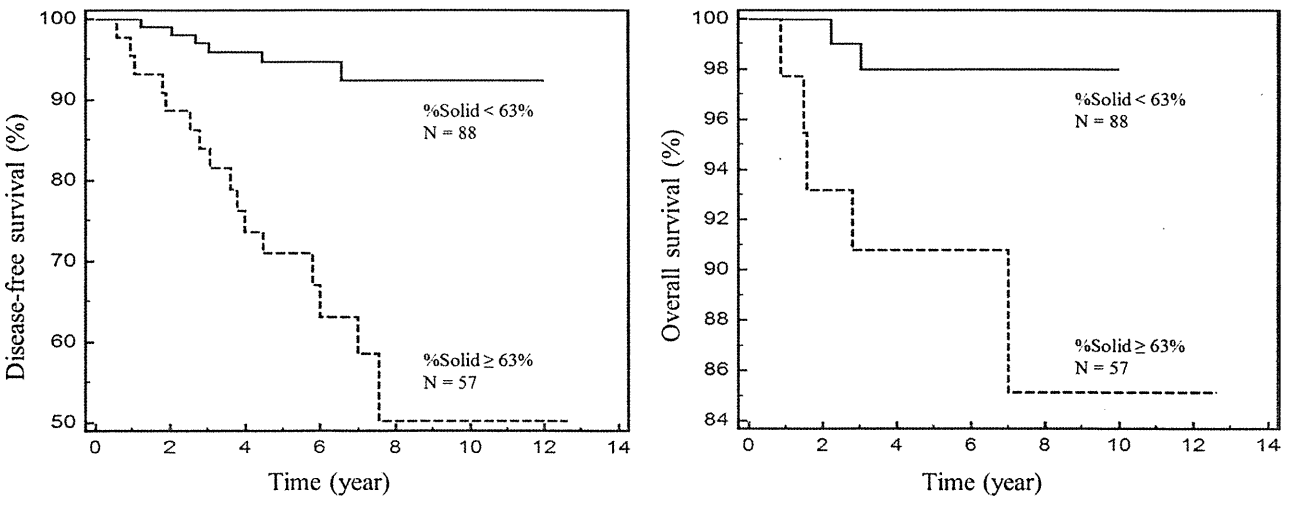

Figure 5: Kaplan-Meier survival curves show that patients with percentage of solid tumor volume of 63% or greater had a significantly lower probability of **(a)** disease-free ($P < .001$) and **(b)** overall survival ($P = .010$) than patients with percentage of solid tumor volume of less than 63%.

Discussion

Clinical algorithms for optimal management of adenocarcinomas that manifest as subsolid nodules by using CT imaging remain an area of active controversy. In two guidelines recently published by the Fleischner Society (6) and American College of Chest Physicians (22), there was disagreement as to whether total diameter or diameter of only the solid component of a part-solid GGN should be used as the predictive feature that determines triage into alternate management pathways. A more fundamental controversy is whether solid tumor components visualized by using CT imaging should be measured on mediastinal or lung windows (23).

In our study, we used a volumetric automated computer-assisted method to analyze early-stage adenocarcinomas and link the analytic output, including volumetric measurements, to prognostic

Table 4

Quantitative Measurements in 22 Patients with Recurrence and Death

Case No.	Longest Diameter of Tumor (mm)	Longest Diameter of Solid Component (mm)	Solid Proportion (%)	Total Volume (cm^3)	Solid Volume (cm^3)	Percentage of Solid Volume (%)	Type of Surgery	Site of Recurrence
Recurrence								
1	13.7	4.8	35.04	1.26	0.48*	38.1†	Seg (LLL)	Lung (RUL)
2	19	16.7	87.89	2.88	2.04	70.8	L (LUL)	Lung (LLL)
3	21.4	18.1	84.58	4.5	2.87	63.8	Seg (LUL)	Lung (LUL)
4	10	10	100	0.45	0.34*	75.6	Seg (RLL)	Lung (multiple)
5	12	12	100	0.82	0.67*	81.7	L (RML)	Lung (RUL)
6	12	12	100	0.9	0.62*	68.9	Seg (LUL)	Lung (RML)
7	13.3	13.3	100	2.38	1.92	80.7	L (RUL)	Lung (LLL)
8	16	16	100	2.04	1.82	89.2	L (RUL)	Lymph node
9	18.5	14.5	78.38	2.44	1.8	73.8	L (LUL)	Bone
10	21	21	100	5.14	3.99	77.6	L (RML)	Lymph node
11	21.5	21.5	100	4.75	4.04	85.1	L (RLL)	Lung (LLL)
12	29.2	29.2	100	12.38	10.55	85.2	L (LLL)	Lymph node
13	18	18	100	3.35	2.92	87.2	L (RLL)	Lung (multiple)
14	19.1	19.1	100	3.28	2.78	84.8	Seg (LLL)	Lung (LUL)
15	22.1	22.1	100	6.53	4.93	75.5	L (RUL)	Lymph node
Death								
16	27.1	15	55.35	9.31	2.77	29.8†	Seg (RUL)	Pleura
17	15.3	10	65.36	0.74	0.48*	64.9	L (LUL)	Brain
18	12	12	100	0.87	0.64*	73.6	Seg (RLL)	Lymph node
19	15.1	15.1	100	4.46	4.01	89.9	L (LUL)	Lung (RUL)
20	18.3	18.3	100	1.95	1.53	78.5	Seg (LUL)	Lung (LUL)
21	19.9	19.9	100	4.09	3.18	77.8	L (RML)	Pleura
22	22.2	22.2	100	6.33	4.69	74.1	L (LLL)	Pleura

Note.—Information in parentheses is excision cite. L = lobectomy, Seg = segmentectomy, RUL = right upper lobe, RML = right middle lobe, RLL = right lower lobe, LUL = left upper lobe, LLL = left lower lobe.

* Volume of solid component was less than 1.5 cm^3.

† Percentage of solid volume was less than 63%.

factors and outcome measures. By using our custom software, automatic classification of nodules had excellent agreement with visual classification by radiologists; pure GGNs classified visually and by using software were associated with excellent prognosis with no recurrences or death observed. The uniformly excellent prognosis of pure GGNs after resection has been reported by several groups (24–26), and we are unaware of any cases of recurrence, even when nodules less than 3 cm of pure ground-glass composition are eventually found at pathologic examination to have invasive components (26).

Accurate segmentation of pulmonary nodules with or without ground-glass component is a challenging problem (27–31). In general, nodule segmentation is performed by using a combination of watershed and shape-analysis techniques; however, because these methods are edge-based, they cannot accurately delineate GGNs that typically share blurred margins with the surrounding lung parenchyma. Tan et al (31) have developed a probability-based method for segmentation of ground-glass nodules by using a Markov random model. By using this technique, the average overlap between computer and manual results for six nodules that contain ground-glass components was 60%. Kim et al (32) demonstrated that volumetric analysis was applicable for volume and mass measurement (12) of both pure and part-solid GGNs without measurement variation. In our study, we elected to segment nodules by using the mean FWHM of multiple density profile curves found by using CT imaging, drawn through the center of each tumor, with recognition that this would be an imperfect but reproducible technique that likely underestimates the extent of peripheral ground glass in some cases of part-solid GGNs. Incorporation of a three-dimensional line filter in our software also allowed for the elimination of both contiguous and intralesional vessels that may artificially increase the calculated total tumor or solid tumor volume measurements, respectively.

Similar to previous studies (4,33–35), we found that for stage I adenocarcinoma, measurement of total tumor was associated less with prognostic factors and outcome than it was with measurements of the solid component. In our study, percentage of solid volume of 63% or greater was associated

Figure 6

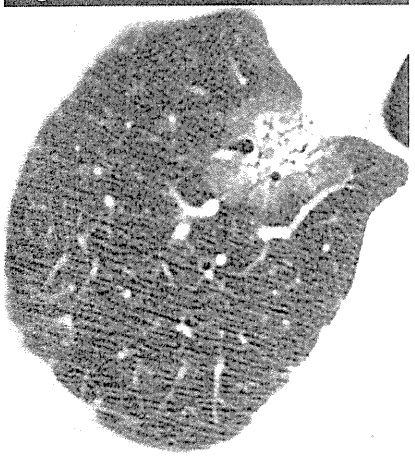

Figure 6: Thin-section CT image of a 27-mm nodule with multiple foci of solid components in a 65-year-old man who eventually died of recurrent disease. Volumetric measurements were total tumor volume, 9.31 cm^3; solid tumor volume, 2.77 cm^3; and percentage of solid tumor volume, 29.8%.

with the presence of pleural invasion; none of the four volumetric measurements were found to be associated with lymphatic or vascular invasion. This latter finding is discordant with results reported by Tsutani et al (33), who found that in 502 patients with clinical stage IA adenocarcinoma, solid tumor diameter was predictive of pleural, as well as of vascular and lymphatic invasion. Difference in results may be related to differences in the enrolled patient populations because our study included patients with pathologic stage I adenocarcinoma without lymph node metastases, and who therefore had a correspondingly lower prevalence of lymphatic invasion, vascular invasion, and pleural invasion compared with the population studied by Tsutani et al.

By using our volumetric automated computer-assisted analytic program, we found two volumetric measurements, solid volume of 1.5 cm^3 or greater and percentage of solid volume of 63% or greater, to be independent indicators associated with recurrence and/or death in patients with stage I adenocarcinoma. These results are consistent with those of previous studies that also reported that features found by using CT imaging, such as maximum diameter of the solid component (4,33) and ratio of maximum diameter of solid to ground-glass components exceeding 50% (2,36), can be associated with tumor recurrence after surgery. In our study, the two volumetric measurements were complementary, and used in combination they correctly identified 21 of 22 (95%) recurrent tumors. However, none of our evaluated two-dimensional measurements were found at multivariate analysis to be independent indicators associated with outcome; this lack of statistically significant results at multivariate analysis likely reflects the high degree of correlation between two-dimensional and volumetric variables and suggests that of the two quantitative sets, volumetric measurements may serve as better indicators associated with outcome. Compared with two-dimensional analysis that typically consists of tumor measurements on one or two images, volumetric analysis enables a more comprehensive and representative evaluation that may be particularly important for adenocarcinomas that have multiple foci of solid components.

Our study had several limitations. The study was retrospective in nature, and the relatively small number of enrolled patients may have resulted in inadequate statistical power to detect some CT features associated with prognosis. Results found in our study that had no statistically significant differences may have been caused by a true lack of differences or by the small sample size. Prospective studies with larger sample sizes will be needed to validate our results. Segmentation of subsolid nodules by using our custom software was imperfect with underestimation of the extent of peripheral ground glass. Given that ground glass is known to correspond to the lepidic noninvasive component of tumor, we chose not to perform manual edits so as to avoid the introduction of observer variability. Computer analysis of nodules was performed by only one operator who was required to select a tumor center point and draw an over-inclusive region of interest around the nodule before automated volumetric measurements could be performed. Ideally, the inclusion of one or more additional operators would have allowed for assessment of the reproducibility of the computer-generated volumetric measurements. Finally, inconsistency in the types of operations may have negatively affected outcomes in some patients who underwent sublobar resection; there are currently two ongoing randomized trials in Japan and North America to address whether segmentectomy can replace lobectomy as standard treatment (1).

In conclusion, our results demonstrated that two volumetric measurements (solid volume of ≥1.5 cm^3 and percentage of solid volume of ≥63%) are independent and complementary indicators associated with recurrence and/or death in patients with stage I adenocarcinoma. These results may have implications for determination of the optimal management of subsolid nodules.

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CURRENT TOPICS REVIEW ARTICLE

Lymph node dissection for lung cancer: past, present, and future

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Abstract In 1978, Naruke et al. proposed an anatomical map that included numbered lymph node stations, which then became widely used for nodal dissection. In 1997, Mountain and Dresler published a new map, which is now favored by the American Thoracic Society and the European Respiratory Society. Using these maps, regional nodal dissection has been universally performed in lung cancer surgery. Clear evidence regarding the survival benefit of lymph node dissection for lung cancer is lacking. However, lobectomy with lymph node dissection continues to be a standard surgical procedure for lung cancer because lymph node dissection is an important investigative process in staging patients. Over the last decade, the extent of nodal dissection for lung cancer has changed due to the increasing number of early detected lung cancers made possible by the recent development of the CT scanner. This manuscript describes the history, present strategy, and future perspectives of lymph node dissection for lung cancer.

Keywords Lymph node dissection · Lung cancer · Mediastinal dissection · Systematic nodal dissection · Systematic sampling

Introduction

In 1960, Cahan [1] reported the first 48 cases to successfully undergo lobectomy with regional lymph node dissection, referred to as "radical lobectomy". Since then, this procedure has been a standard surgery for lung cancer treatment. In 1978, Naruke et al. [2] proposed an anatomical map that included numbered lymph node stations, which then became widely used for nodal dissection. In 1997, Mountain and Dresler [3] published a new map, which is now favored by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) [4, 5] and was adopted in the Union Internationale Contre le Cancer (UICC) TNM atlas. Using these maps, regional nodal dissection, including the superior and inferior mediastinum, has been universally performed in lung cancer surgery. However, over the last decade, the extent of nodal dissection for lung cancer has changed due to the increasing number of early detected lung cancers made possible by the recent development of the CT scanner. The present manuscript describes the history, present strategy, and future perspectives of lymph node dissection for lung cancer.

Historical perspectives

In 1951, Cahan [6] suggested that pneumonectomy and hilar and mediastinal lymph node dissection—collectively referred to as "radical pneumonectomy"—should be a standard surgery for patients with lung cancer. Nine years later, Cahan [1] reported the first 48 cases that successfully underwent lobectomy with regional lymph node dissection, termed "radical lobectomy." Following that report, this procedure was universally accepted and has remained a standard surgery for lung cancer for more than half century. Detailed lobe-specific lymphatic pathways were reported in 1956 by Nohl [7]. In 1978, Naruke et al. [2] suggested the use of an anatomical map in which the lymph node stations were numbered, with numbers 1–9 used to designate mediastinal (N2) stations, and numbers 10–14 for N1

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stations. This map was intended to be a visual aid to ensure uniform recording of the various lymph nodes stations involved in tumor progression in lung cancer patients. The Japan Lung Cancer Society adopted this map and established detailed definitions for each nodal station in their manual for the Classification of Lung Cancer [8].

In 1996, meticulous evaluation of nodal involvement at the mediastinal and hilar levels was termed "systematic nodal dissection" (SND) by the International Association for the Study of Lung Cancer (IASLC) [9]. The IASLC task force discarded the term "radical" as it inferred some therapeutic benefit from this evaluation. The term "mediastinal" was also discarded to avoid discounting the importance of evaluating N1 nodes. Since then, this technique has been accepted as an important component of intrathoracic staging by all thoracic surgeons [9]. Recently, some multi-institutional clinical trials evaluating the significance of adjuvant chemotherapy in patients with lung cancer have demonstrated a survival benefit of postoperative chemotherapy for stage II and IIIA patients [10, 11], thus highlighting the importance of SND. A consensus in favor of SND could unify the nomenclature and establish the minimal technical requirements for nodal dissection in lung cancer surgery.

Table 1 Definitions of lymph node dissection for lung cancer (ESTS guidelines) [12]

Term	Definition
Systematic nodal dissection (SND)	All the mediastinal tissues containing the lymph nodes are dissected and removed systematically within anatomical landmarks.
Selected lymph node biopsy	One or multiple suspicious lymph node(s) are biopsied. This is only justified to prove N1 or N2 disease in patients in whom resection is not possible (exploratory thoracotomy).
Sampling	Removal of one or more lymph nodes guided by preoperative or intraoperative findings which are thought to be representative.
Systematic sampling (SS)	Predetermined selection of the lymph node stations specified by the surgeon.
Lobe-specific systematic node dissection	The mediastinal tissue containing specific lymph node stations are excised, depending on the lobar location of the primary tumor.
Extended lymph node dissection	Bilateral mediastinal and cervical lymph node dissection is performed through median sternotomy and cervicotomy.

Definitions of lymph node dissection

Lymphadenectomy for lung cancer can be performed using a variety of procedure types and extents of dissection (Table 1). European Society of Thoracic Surgeons (ESTS) guidelines have defined SND as requiring the dissection and removal of all mediastinal tissue containing the lymph nodes within anatomical landmarks [12] (Fig. 1). The ESTS guidelines recommend that SND involves a minimal excision of at least three mediastinal nodal stations, including the subcarinal node [12]. The term "sampling" is used to describe a lesser excision of certain nodal stations that seem to be representative or abnormal in preoperative evaluations or intraoperative findings. Gajra et al. [13], Doddoli et al. [14], and Massard et al. [15] have suggested that sampling is inferior to SND in terms of proper staging. Finally, the term "systematic sampling" refers to a routine biopsy of lymph nodes at some levels of nodal station specified by the surgeon [12, 16]. Keller et al. [16] and Gajra et al. [13] reported that systematic sampling was as effective as SND for accurately staging patients.

Importance of lymph node dissection for accurate staging

Surgeons have long known that the situation found at thoracotomy is not always as predicted by preoperative investigations using CT and positron emission tomography (PET). Meta-analyses have shown that the use of CT for assessing mediastinal nodal involvement has a sensitivity on the order of 60–83 %, specificity of 77–82 %, and negative predictive value (NPV) of 85–86 % [17–19]. PET is considered to be the most sensitive and accurate non-invasive means of screening for lymph node involvement, with meta-analysis results showing a sensitivity of 79–88 %, specificity of 90–92 %, and NPV of 93–94 % [18–20]. Overall, the assessment of nodal status by CT and PET is not reliable enough in patients with microscopic nodal metastasis, and thus the intrathoracic evaluation of nodal involvement at the mediastinal and hilar levels during thoracotomy is considered an important component of the staging process [21].

Since the pathological nodal status is reportedly the most significant prognostic factor [22, 23], pathological examination of dissected lymph nodes offers the most precise information for prognosis in patients with lung cancer. Among patients with adenocarcinomas at the National Cancer Center Hospital, 60 % of cases diagnosed as cN1 disease by chest CT were pathologically diagnosed as N2 disease after thoracotomy [24]. Graham et al. [25] suggested that SND could disclose "unexpected" N2 disease irrespective of cell type, size, and location of the primary tumor, and regardless of whether prior mediastinoscopy had been performed. Although the results were referred from reports published late 1990 and early 2000

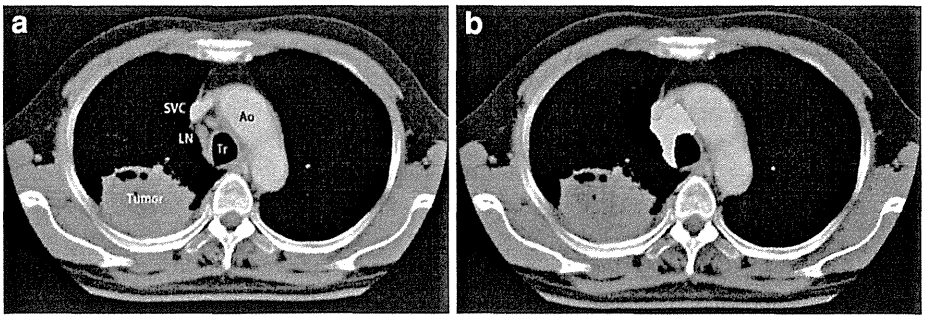

Fig. 1 CT images demonstrating differences in the extent of nodal dissection and sampling. **a** Superior mediastinal lymph nodes and surrounding fatty tissue. *SVC* superior vena cava, *LN* superior mediastinal lymph node (#4R), *Tr* trachea, *Ao* aorta. **b** Extent of lymph node dissection (*yellow color area*)

during the era PET and EBUS were not available yet, even small-sized lung cancer (<2 cm) shows hilar and mediastinal nodal disease with an incidence of more than 20 % [26, 27]. Furthermore, N2 lung cancer patients exhibit a 20–38 % incidence of a phenomenon termed "skip metastasis" in which N2 disease occurs without N1 involvement [28–32]. These facts support the importance of SND at the mediastinal and hilar levels during thoracotomy.

Several recent multi-institutional clinical trials evaluating the effects of adjuvant chemotherapy in patients with lung cancer have demonstrated a survival benefit of postoperative chemotherapy for node-positive patients [10, 11]. A significant survival benefit of adjuvant chemotherapy was also observed in the lung adjuvant cisplatin evaluation (LACE) meta-analysis—which was based on individual patient data collected from the five largest trials (4,584 patients) of cisplatin-based adjuvant chemotherapy in completely resected patients with NSCLC—with an overall hazard ratio (HR) of 0.89, translating into a 5 years absolute survival benefit of 5.4 % [33]. The benefit of chemotherapy varies with tumor stage, with results showing adjuvant chemotherapy to be detrimental for stage IA disease (HR for death, 1.40; 95 % CI, 0.95–2.06), of unclear benefit for stage IB tumors (HR for death, 0.93; 95 % CI, 0.78–1.10), but clearly beneficial for patients with resected disease of stage II (HR for death, 0.83; 95 % CI, 0.73–0.95) or III disease (HR for death, 0.83; 95 % CI, 0.72–0.94) [33]. Based on these studies, adjuvant platinum-based chemotherapy has become standard care for patients who undergo resection of stage II or III NSCLC. The accurate identification of positive nodes is important for selection of the optimal therapy and better determining patient prognosis [13, 14].

For the aforementioned reasons, it is thought that an accurate pathologic assessment for metastasis to the lymph nodes has many advantages for patients with lung cancer. According to the results of ACOSOG Z0030 trial [34], 4 % of additional patients were found to have lymph node metastases after SND that were missed at meticulous systematic sampling (2R, 4R, 7 and 10R for right side, and 5, 6, 7 and 10L for left side). Since SND can reveal "unexpected" N_2 disease—irrespective of cell type; the size, location, and lobe of origin of the primary tumor; and whether or not prior mediastinoscopy was performed—SND remains an important investigative process in all patients receiving surgery for lung cancer.

Potential survival benefit from lymph node dissection

Even in stage I patients, the most frequent relapse pattern after complete resection for lung cancer is distant metastasis, often due to a distant micrometastasis that already existed at the time of surgery. Lymph node dissection is a therapy used to achieve better local control of cancer, and thus does not improve the survival of patients with distant metastasis. Moreover, in a patient without nodal metastasis, lymph node dissection can only prove the pathological N0 status and has no impact on survival. Therefore, the patients who can obtain survival benefit from SND are those with resectable pN1 and pN2 disease and no distant micrometastasis, who may comprise only a small subset of patients with lung cancer. Evaluating this potential survival benefit is complicated by the challenge of preoperatively recognizing and randomizing patients with microscopic N2, which can generally only be identified after completion of nodal dissection and pathological examination [35–39]. Therefore, to demonstrate the oncological benefit of lymph node dissection in a RCT, extremely large numbers of patients must be enrolled in the study.

Several reports have suggested that lymph node dissection could improve survival in some cases. In a non-randomized trial, Keller et al. [16] compared patients with resected stage II–IIIA NSCLC who underwent SND or systematic sampling, and found significantly improved survival among those with SND. While Lardinois et al. [40] showed no significant difference of survival between the patient who underwent SND or systematic sampling (Table 2). Several retrospective non-randomized studies have also shown a survival benefit of nodal dissection [41–45]. However, the survival benefit of lymph node

Table 2 Prospective non-randomized studies compared the long-term results of systematic nodal dissection (SND) and sampling

Author	Year reported	Patient	Number of patient (SND/sampling)	Median follow-up time	Results (SND/sampling)
Keller [16]	2000	Completely resected stage II–IIIA NSCLC	373 (186/187)	44 months	Median survival 57.5/29.2 months, $p = 0.004$
Lardinois [40]	2005	Clinical T1-3N0-1M0 NSCLC	100 (50/50)	89 months	Median survival 51.7/50.9 months, $p = 0.4$

Table 3 Prospective randomized studies compared the long-term results of systematic nodal dissection (SND) and sampling

Author	Year reported	Patient	Number of patient (SND/sampling)	Median follow-up time	Results (SND/sampling)
Izbicki [46]	1998	Operable NSCLC	169 (76/93)	47.5 months	HR = 0.76, $p = 0.273$
Sugi [47]	1998	Peripheral NSCLC less than 2 cm in size	115 (59/56)	65 months	5-year survival rate 81.4 %/83.9 %, $p =$ NS
Wu [48]	2002	Clinical stage I–IIIA NSCLC	471 (240/231)	NA	5-year survival rate 48.4 %/37.0 %, $p = 0.0000$
Darling [34]	2011	N0 or non-hilar N1 NSCLC	1023 (525/498)	6.5 years	Median survival 8.5/8.1 years, $p = 0.25$

dissection has not yet been clearly statistically proven for patients with lung cancer, simply because few prospective randomized controlled trials (RCTs) have compared SND with nodal sampling (Table 3). Izbicki et al. [46] reported no significant difference in survival between patients with clinical stage I–IIIA lung cancer who underwent systematic nodal dissection and nodal sampling. However, it is possible that the number of enrolled patients in each arm (SND vs. sampling; $n = 76$ vs. 93) was insufficient, as over half of the subjects were found to be node-negative in the pathological examination. Sugi et al. [47] reported no significant difference in survival between patients with lung cancer of <2 cm who underwent mediastinal dissection or sampling. However, this study also included only a very small number of patients (59 SND vs. 56 sampling).

In the only prospective randomized study to suggest a survival benefit of nodal dissection, Wu et al. [48] investigated 532 patients, and reported significantly better survival in the SND group ($n = 268$) compared to the sampling group ($n = 264$). Wright et al. [49] performed a meta-analysis of these three randomized RCTs, comparing SND and sampling. They found a significant reduction in the risk of death in the group undergoing SND, with a hazard ratio estimated at 0.78 (95 % CI 0.65–0.93; $p = 0.005$). Detterbeck [50] reviewed the intraoperative management of patients with "surprise N2," a term used to describe microscopic N2 disease. Based on the results of the above-mentioned randomized studies, he concluded that resection was justified for this subset unless it was apparent that disease would be left behind. However, the description of the randomization method in these three studies is insufficient according to the CONSORT statement [51]. The American College of Surgery Oncology Group (ACOSOG) Z0030 study—a multi-institutional prospective randomized trial designed to compare the long-term survival after SND and sampling—recently reported no significant differences between those two groups [34]. This study showed that SND did not improve survival in patients with pathologically negative hilar and mediastinal lymph nodes after systematic sampling. However, the sampling performed prior to the randomization in this study (2R, 4R, 7 and 10R for right side, and 5, 6, 7 and 10L for left side) was similar to the SND rather than the sampling procedure in our daily practice. Therefore, we must be careful to interpret the results of this study.

Collectively, the available data leave it unknown whether lymph node dissection has a survival benefit. Conducting a multi-institutional very large RCT evaluating a survival benefit of SND actually will be quite difficult and not realistic.

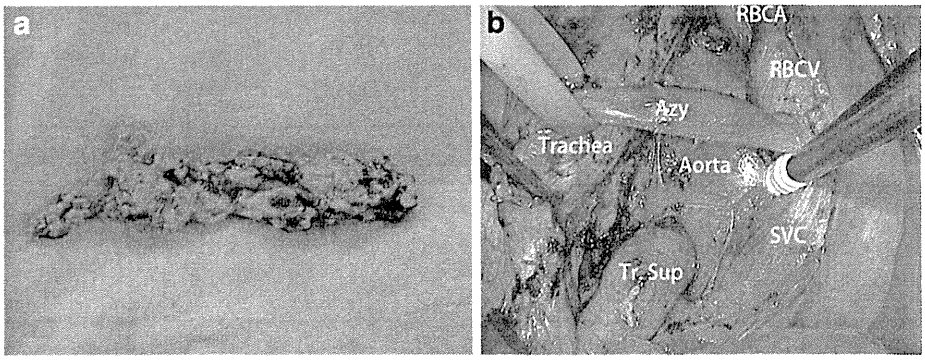

Fig. 2 Photographs taken following systematic nodal dissection of the right superior mediastinum. **a** Removed lymph nodes and surrounding fatty tissue *en block* within anatomical landmarks. **b** Skeletonized anatomic structures after systematic nodal dissection. *SVC* superior vena cava, *Tr. Sup* superior trunk of the right pulmonary artery, *RBCV* right brachiocephalic vein, *RBCA* right brachiocephalic artery, *Azy* azygos arch

Table 4 A proposal of the strategy of selective nodal dissection based on segment-specific patterns of nodal spread [53]

	RUL LUL-superior	RML LUL-lingular	RLL-superior LLL-superior	RLL-basal LLL-basal
Superior mediastinal (#1-4) or aortic (#5, 6) nodes[c]	Advisable	Advisable	Advisable	Not always necessary[b]
Inferior mediastinal nodes				
Subcarinal node (#7)	Not always necessary[a]	Advisable	Advisable	Advisable
Paraesophageal (#8) and pulmonary ligament (#9) nodes	Unnecessary	Unnecessary	Advisable	Advisable

[a] Unnecessary if pretracheal node (#4R) is negative on frozen section

[b] Unnecessary if subcarinal node (#7) is negative on frozen section

[c] Superior mediastinal nodes for right side and Aortic nodes for left side

Technical concept of lymph node dissection

Regarding technical aspects of SND, it is carried out by excising all tissue in the compartment surrounded by some anatomic structures. The modern procedure remains similar to that reported by Cahan in 1951 [6]. As shown in Fig. 2, the process should include en block removal of all tissue that may contain cancer cells, including lymph nodes and surrounding fatty tissue within anatomical landmarks, as well as the trachea, bronchus, superior vena cava, and the aorta and its branches, pulmonary vessels, and pericardium. These procedures are performed mainly with scissors or electrocautery; however, ligation of the connective tissue, possibly including the small lymphatic vessels, is sometimes necessary to prevent postoperative chylothorax.

Changes in the extent of lymph node dissection

The extent of lymph node dissection for lung cancer has also changed little since Cahan reported "radical lobectomy" in 1960 [1]. SND involves the identification of nodal stations and labelling them in accordance with an internationally recognized nodal chart. Several lymph node maps have been proposed [2, 3], each with its advantages and disadvantages [52]. The most widely used map is that proposed by Naruke in 1978 [2]. In 1997, Mountain and Dresler [3] published a new map, which has been favored by the ATS and the ERS [4, 5], and which was included in the American Joint Committee on Cancer (AJCC) handbook and in the UICC TNM atlas [53]. With these maps, regional nodal dissection including the superior and inferior mediastinum has been universally performed in lung cancer surgery [13, 14, 54].

In recent years, nodal dissection has often been performed more selectively by considering the tumor location-specific lymphatic pathway, especially for cases of early cancer with less extensive nodal involvement. Advanced analyses of the lymph node metastatic pathway have led to recognition of lobe-specific or even segment-specific patterns of nodal metastases. Asamura et al. [55] and Okada et al. [56] reported that right-upper lobe tumors and left-upper segment tumors tend to metastasize to the superior mediastinum, but rarely metastasize to the subcarinal nodes without concomitant metastasis to the hilar or superior mediastinal nodes. Additionally, Okada et al. [57] suggested that lower-lobe tumors seldom metastasize to the superior mediastinal nodes without concomitant metastasis

to the hilar or subcarinal nodes. Even the results of segment-specific lymphatic pathways based on the analysis of nodal spread patterns in N2 patients were reported [58]. This knowledge of tumor location-specific patterns of nodal metastases has changed the preoperative evaluation of nodal status and the strategies of nodal dissection, especially in stage I lung cancer (Table 4) [56–60]. As early detection of lung cancer becomes more common, the extent of nodal dissection should be tailored to the individual case, for example, by considering the tumor location, tumor size, cell type, and percentage of ground glass opacity (GGO) area on CT scan in each tumor. This type of tailored dissection—termed "lobe-specific SND" by ESTS guidelines [12]—involves the investigation of only the "key nodes" based on the tumor's lobal location [55–60]. A subcommittee of the IASLC staging committee has proposed a definition of complete resection for lung cancer that includes the requirements of no residual tumor after SND or lobe-specific SND [61].

Conclusion

Establishing the survival benefit of nodal dissection in lung cancer surgery will be very challenging because of the difficulty in carrying out large RCT studies and the lack of appropriate methodology. Clear evidence regarding the survival benefit of lymph node dissection for lung cancer is lacking. However, lobectomy with lymph node dissection continues to be a standard surgical procedure for lung cancer because lymph node dissection is an important investigative process in staging patients and takes just 20–30 min [39, 62]; Since the initial results of the ACOSOG Z0030 randomized trial [63] found no increase in morbidity or mortality from lymph node dissection, there appears to be little benefit in limiting nodal dissection.

Conflict of interest The author has declared that no conflict of interest exists.

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ORIGINAL ARTICLE

THORACIC

Impact of the epidermal growth factor receptor mutation status on the post-recurrence survival of patients with surgically resected non-small-cell lung cancer†

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Abstract

OBJECTIVES: The impact of epidermal growth factor receptor (EGFR) status and the use of EGFR-tyrosine kinase inhibitor (EGFR-TKI) therapy have not been well discussed only in recurrent non-small-cell lung cancer (NSCLC). The purpose of this study was to identify the prognostic factors associated with post-recurrence survival after surgical resection of NSCLC in terms of the EGFR mutation status and the use of EGFR-TKI therapy.

METHODS: From 2000 through 2011, 1237 consecutive patients with NSCLC underwent pulmonary resection at our institution. Of these patients, 280 experienced postoperative recurrence by the end of 2012. We reviewed the cases of recurrence and analysed the predictors and length of post-recurrence survival.

RESULTS: The median post-recurrence survival time and the 5-year survival rate of all patients were 25 months and 20.8%, respectively. A multivariate analysis identified the Eastern Cooperative Oncology Group (ECOG) performance status (PS), brain metastasis, number of sites of recurrence and EGFR mutation status to be independent prognostic factors for post-recurrence survival. Among all cases, the median post-recurrence survival time according to the use of EGFR-TKI therapy was as follows: 49 months in the EGFR mutation-positive patients treated with EGFR-TKI therapy, 20 months in the EGFR wild or unknown cases treated with EGFR-TKI therapy and 17 months in the patients not treated with EGFR-TKI therapy. As to EGFR mutation-positive cases, the patients treated with EGFR-TKIs exhibited significantly longer post-recurrence survival time than the patients treated without EGFR-TKIs (49 vs 12 months).

CONCLUSIONS: It is essential for recurrent NSCLC patients to be examined for the EGFR mutation status. Patients with a positive EGFR mutation status receive significant benefits from EGFR-TKI therapy.

Keywords: Non-small-cell lung cancer • Surgical resection • Post-recurrence survival • EGFR mutation • EGFR-TKIs

INTRODUCTION

Lung cancer continues to be the most frequently occurring type of cancer, with approximately 1.61 million new cases each year. Non-small-cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancer cases [1]. Although surgery is the best therapeutic modality for patients with early stage NSCLC, recurrence is reported in 20–50% of all cases [2–9].

Treatment for recurrent disease is usually similar to that used for advanced disease; however, considering the diversity of recurrent disease and the postoperative state, there remains controversy regarding whether the standard treatment for advanced disease should be the standard treatment for recurrent disease. Chemotherapy and radiation therapy are commonly accepted treatment options for recurrent lung cancer, and several authors have described the effects of surgical resection in patients with recurrent disease [9–11]. On the other hand, no standard therapeutic policy for treating recurrent disease has been established. In addition, the post-recurrence survival of surgically treated NSCLC patients has been examined less often than the overall or disease-free survival of patients with advanced disease.

Epidermal growth factor receptor (EGFR) is a receptor kinase that is highly expressed in cancer cells. Mutations in the EGFR gene that are frequently present in exons 18–21 have been reported to be critical gene mutations in the setting of NSCLC

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[12-14]. EGFR-tyrosine kinase inhibitors (EGFR-TKIs) such as gefitinib and erlotinib have been used to treat NSCLC, showing extremely good responses in some populations of NSCLC patients [15-17]. The development of these medicines has caused a major change in therapeutic strategies for treating advanced and recurrent disease. On the other hand, the impact of these medicines has not been well documented particularly for recurrent disease.

The purpose of this study was to identify the prognostic factors associated with post-recurrence survival after surgical resection of NSCLC and to examine the best therapeutic strategy for treating this disease based on the EGFR mutation status and the use of EGFR-TKI therapy.

MATERIALS AND METHODS

Patients

A total of 1237 consecutive patients who underwent surgical resection for NSCLC at the National Kyushu Cancer Center between January 2000 and December 2011 formed the initial study cohort. By the end of 2012, 280 patients from the cohort were identified as having recurrent disease.

Postoperative follow-up and diagnosis of recurrence. A follow-up examination was usually performed every 2-3 months for the first 2 years, then every 3-6 months thereafter. The routine follow-up procedures included a physical examination, haematological examination and chest radiography. In addition, chest and abdominal computed tomography was performed at least once a year. When recurrent disease was suspected, further examinations, such as brain magnetic resonance imaging, bone scintigraphy and fluorodeoxyglucose-positron emission tomography were added. Recurrent NSCLC was diagnosed based on physical examination results and diagnostic imaging findings of lesions consistent with recurrent disease. Differentiating between a second primary lung cancer and intrapulmonary metastasis was, in general, performed according to the definitions proposed by Martini and Melamed [18]. Histological confirmation of the diagnosis was obtained when clinically feasible. The date of recurrence was defined as the date of histological confirmation or, in cases diagnosed based on clinical evidence, the date of recognition of recurrent disease by the attending physician. Local recurrence was defined as disease recurrence at the surgical margin, ipsilateral hemithorax or mediastinum. Distant metastasis was defined as disease recurrence in the contralateral lung or outside of the hemithorax and mediastinum.

Data collection and extraction. Demographic, clinical and treatment data were abstracted from an institutional database that included all patients who had undergone thoracic surgery. The histological diagnosis of the tumours was made based on the criteria of the World Health Organization, [19] and the TNM Classification of Malignant Tumors (TNM) stage was determined according to the criteria revised in 2009 [20]. EGFR mutations were detected using direct sequencing or a highly sensitive PCR-based analysis. Deletion mutations in exon 19 and point mutations in exon 18 or exon 21 were considered to be EGFR

Table 1: Characteristics of the patients

Variables	No. (%)	HR (95% CI)	*P*-value
Age (years)			
<70	168 (60)	0.98 (0.72-1.33)	0.89
≥70	112 (40)	1.00 (-)	
Gender			
Male	183 (65)	1.49 (1.09-2.05)	0.01
Female	97 (35)	1.00 (-)	
Performance status			
0-1	241 (86)	0.19 (0.13-0.28)	<0.01
2-4	39 (14)	1.00 (-)	
Smoking status			
Pack year index ≥20	159 (57)	1.36 (1.01-1.84)	0.04
Pack year index <20	121 (43)	1.00 (-)	
Histological type			
Squamous cell carcinoma	51 (18)	1.85 (1.27-2.70)	<0.01
Others	40 (14)	1.75 (1.15-2.66)	
Adenocarcinoma	189 (68)	1.0	
Pathological stage (TNM seventh edition)			
I	96 (34)	1.05 (0.55-2.02)	0.18
II	59 (21)	1.15 (0.58-2.27)	
III	107 (38)	1.49 (0.79-2.81)	
IV	18 (7)	1.0 (-)	
EGFR mutation			
Positive	83 (30)	0.36 (0.25-0.54)	<0.01
Wild	100 (36)	0.71 (0.51-0.99)	
Unknown	97 (34)	1.0 (-)	
Disease-free interval			
≥1 year	130 (46)	0.76 (0.57-1.02)	0.07
<1 year	150 (54)	1.0 (-)	

HR: hazard ratio; 95% CI: 95% confidence interval; EGFR: epidermal growth factor receptor.

mutations in this study. Written informed consent was obtained from each patient to use their medical records. The institutional review board provided approval for this study.

Statistical analysis. Length of post-recurrence survival was measured from the date of initial recurrence to the date of death from any cause or date on which the patients was last known to be alive. The probability of survival was estimated using the Kaplan–Meier method. Differences in survival were evaluated by using log-rank test. Significant variables on post-recurrence survival under the univariate analysis were tested with a multivariate analysis using a Cox proportional hazards regression model. Statistical analyses were performed using JMP software package (SAS Institute, Inc). All *P*-values less than 0.05 were considered to be statistically significant.

RESULTS

Characteristics of the patients

The characteristics of the patients are summarized in Table 1. Postoperative recurrence occurred in 183 males (65%) and 97 females (35%). The median age of the patients was 66 years (range, 34–92 years) and 241 patients (86%) had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 at time of the diagnosis of the initial recurrence. Adenocarcinoma accounted for 68% ($n = 189$) of the cases, followed by squamous cell carcinoma ($n = 51$, 18%) and other histological types ($n = 40$, 14%). Two hundred and fifty-eight patients underwent complete resection and 22 underwent incomplete resection. Two hundred and twenty-two patients underwent lobectomy, 51 underwent pneumonectomy and 6 were treated with limited resection. The pathological stage according to the TNM seventh edition at the time of surgery was Stage I in 96 patients (34%), Stage II in 59 (21%), Stage III in 107 (38%) and Stage IV in 18 (7%). The EGFR mutation status was assessed in 183 cases (65%) and 83 patients (30%) were positive for mutations. Seventy-nine EGFR-positive cases involved adenocarcinoma, 1 involved squamous cell carcinoma and 3 involved other histological types. A univariate analysis determined that gender, ECOG PS, smoking status, histological type and EGFR mutation status influenced post-recurrence survival (Table 1). The median disease-free time from detection of the first recurrence was 12 months (range, 1–84 months). The recurrent form and recurrent site information are shown in Table 2. The most commonly involved organ was the lungs in 97 cases followed by the lymph nodes in 96, bone in 50, brain in 36, liver in 17 and adrenal glands in 15. Among the 280 patients, 90 (32%) had local recurrence, 114 (41%) had distant recurrence and 76 (27%) had both local and distant recurrence. Recurrence in multiple stations was detected in 116 cases (41%). The patients with brain metastasis and multiple station recurrence exhibited significantly worse outcomes than their counterparts (Table 2).

Table 2: Recurrent form and recurrent site

Variables	No. (%)	HR (95% CI)	*P*-value
Recurrent organ			
Lung	97 (35)	0.91 (0.67–1.24)	0.55
Lymph node	96 (35)	1.17 (0.86–1.59)	0.30
Bone	50 (18)	1.14 (0.77–1.68)	0.51
Brain	36 (13)	1.51 (1.01–2.25)	0.04
Adrenal	15 (5)	1.10 (0.58–2.10)	0.76
Liver	17 (6)	1.77 (0.98–3.18)	0.06
Recurrent site			
Local recurrence	90 (32)	0.68 (0.47–1.0)	0.14
Distant recurrence	114 (41)	0.81 (0.57–1.15)	
Both local and distant recurrence	76 (27)	1.0 (–)	
Number of recurrent foci			
Multistation	116 (41)	1.52 (1.13–2.05)	<0.01
Single station	164 (59)	1.0 (–)	

HR: hazard ratio; 95% CI: 95% confidence interval.

Table 3: Treatment for initial recurrence

	No. (%)	Median survival months	HR (95% CI)	*P*-value
Chemotherapy	152 (54)	32 (1–96)	1.08 (0.56–2.07)	0.09
Radiotherapy	32 (12)	20 (1–54)	1.89 (0.90–3.98)	
Chemotherapy with radiotherapy	62 (22)	24 (1–102)	1.36 (0.68–2.68)	
Surgical treatment	15 (5)	37 (14–68)	1.0 (–)	

HR: hazard ratio; 95% CI: 95% confidence interval.

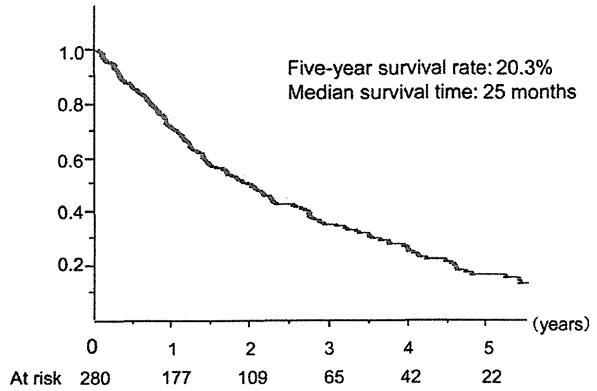

Figure 1: Kaplan–Meier curves of post-recurrence survival in all patients with recurrent NSCLC. The median survival time was 25 months and the 5-year survival rate of all patients was 20.3%. NSCLC: non-small-cell lung cancer.

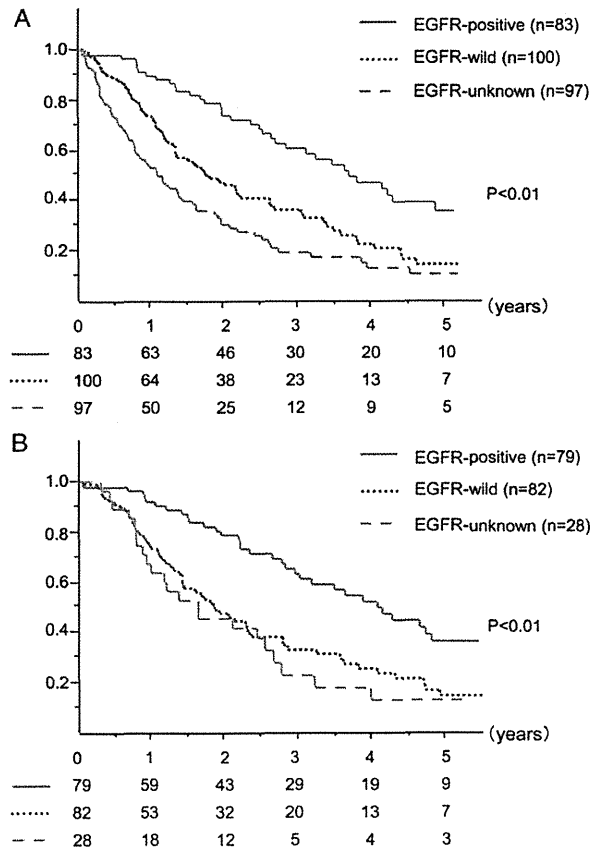

Figure 2: Kaplan–Meier curves of post-recurrence survival according to the EGFR mutation status in (**A**) all cases and (**B**) the adenocarcinoma cases. Solid line: EGFR mutation-positive cases; dotted line: EGFR mutation wild cases; dashed line: EGFR mutation unknown cases. EGFR: epidermal growth factor receptor.

As the initial treatment for recurrence, chemotherapy was performed in 152 patients (54%), chemoradiotherapy was performed in 62 (22%), radiotherapy was performed in 32 (12%) and surgical resection was performed in 15 (5%) (Table 3). The remaining 19 patients (7%) received supportive care only. There were no

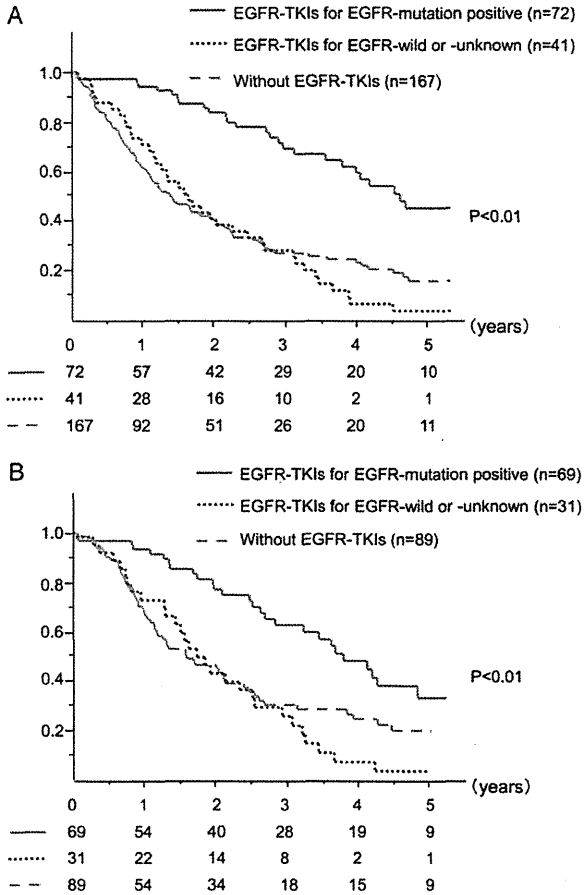

Figure 3: Kaplan–Meier curves of post-recurrence survival according to the EGFR-TKIs therapy in (**A**) all cases and (**B**) the adenocarcinoma cases. Solid line: EGFR-TKIs in EGFR mutation-positive cases; dotted line: EGFR-TKIs in EGFR mutation wild or unknown cases; dashed line: patients treated without EGFR-TKIs. EGFR: epidermal growth factor receptor; EGFR-TKI: EGFR-tyrosine kinase inhibitor.

significant differences among the patients according to the initial treatment strategy (Table 3).

Survival analysis. The median post-recurrence survival time and 5-year survival rate of all patients were 25 months and 20.3%, respectively (Fig. 1). The association between post-recurrence survival and the EGFR mutation status is shown in Fig. 2. The median post-recurrence survival time was 44 months in the patients with an EGFR mutation-positive status, 21 months in the patients with a wild status and 15 months in the patients with an unknown status ($P < 0.01$) (Fig. 2A). As to the adenocarcinoma cases, the median post-recurrence survival time was 44 months in the patients with an EGFR mutation-positive status, 21 months in the patients with a wild status and 20 months in the patients with an unknown status ($P < 0.01$) (Fig. 2B). Among all cases, the median post-recurrence survival time according to the use of EGFR-TKI therapy was as follows: 49 months in the EGFR mutation-positive patients treated with EGFR-TKI therapy, 20 months in the EGFR wild or unknown patients treated with EGFR-TKI therapy and 17 months in the patients not treated with EGFR-TKI therapy ($P < 0.01$) (Fig. 3A). With regard to the adenocarcinoma patients, the median post-recurrence survival time according to the EGFR-TKI therapy was 49, 23 and 20

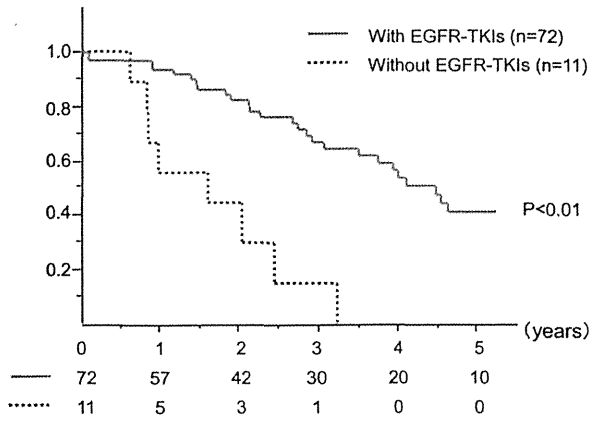

Figure 4: Kaplan–Meier curves of post-recurrence survival in the patients with an EGFR mutation-positive status. Solid line: with EGFR-TKIs; dotted line: without EGFR-TKIs. EGFR: epidermal growth factor receptor; EGFR-TKI: EGFR-tyrosine kinase inhibitor.

Table 4: *Multivariate analysis of predicting factor for post-recurrent survival*

Factors	Multivariate analysis		
	HR	95% CI	*P*-value
Gender			
Male	1.07	0.73–1.57	0.72
Female	1.0		
ECOG PS			
2–4	4.50	3.03–6.69	<0.01
0–1	1.0		
Smoking status			
Pack year index ≥20	1.10	0.78–1.57	0.59
Pack year index <20	1.0		
Histology			
Squamous cell carcinoma	1.59	0.99–2.54	0.11
Others	1.40	0.89–2.19	
Adenocarcinoma	1.0		
Recurrent site			
Multistation	1.43	1.05–1.94	0.02
Single station	1.0		
Brain metastases			
Yes	1.68	1.11–2.54	0.01
No	1.0		
EGFR mutation status			
Positive	0.50	0.31–0.80	<0.01
Wild	0.85	0.58–1.26	
Unknown	1.0		

HR: hazard ratio; 95% CI: 95% confidence interval; EGFR: epidermal growth factor receptor; ECOG PS: Eastern Cooperative Oncology Group performance status.

months, respectively ($P < 0.01$) (Fig. 3B). As to the EGFR mutation-positive cases, the median post-recurrence survival time was 49 months in the patients treated with EGFR-TKIs and 12 months in the patients without EGFR-TKIs. The patients treated with EGFR-TKIs exhibited significantly longer post-recurrence survival time than the patients treated without EGFR-TKIs ($P < 0.01$) (Fig. 4).

A multivariate analysis identified the ECOG PS, brain metastasis, number of sites of recurrence and EGFR mutation status to be independent predictive factors for post-recurrence survival ($P < 0.01$, 0.01, 0.02 and <0.01, respectively) (Table 4).

DISCUSSION

In this study, we retrospectively investigated various aspects of the predictive factors for post-recurrence survival in resected NSCLC patients, particularly focusing on the EGFR mutation status and the use of EGFR-TKI therapy. Several studies have demonstrated predictive factors of post-recurrence survival in resected NSCLC patients [2–11]. Hung *et al.* and Sugimura *et al.* reported that the disease-free survival and treatment for the initial recurrence are prognostic predictors of post-recurrence survival [2, 9]. The site of recurrence and recurrent organs, such as extrathoracic regions, the liver, brain and so on, have also been reported to be predictive factors for post-recurrence survival [5, 6, 9]. Previous studies have demonstrated that local therapies such as radiotherapy and surgical resection succeed in improving the prognosis of selected patients with recurrent disease [9–11, 21]. When recurrence is diagnosed to be local, local therapy has been administrated based on indefinite standards at many facilities including our institution. In this study, some of the patients received local therapies, such as surgical resection, radiotherapy and chemoradiotherapy. The patients who received anticancer treatments for initial recurrence exhibited significantly better outcomes than those who received supportive care only. On the other hand, there were no significant differences in prognosis between the patients treated with these different local therapeutic modalities. The superiority of local therapy was not demonstrated in this study. Most previous studies of local therapy did not include the EGFR mutation status or the use of EGFR-TKI therapy in the analyses. Considering the efficacy of EGFR-TKI therapy for advanced or recurrent disease [15–17], the presence of EGFR mutations should be included as a predictor of post-recurrence survival. In addition, the value of local therapy should be evaluated with due consideration of the EGFR mutation status and the use of EGFR-TKI therapy.

Recently, some studies reported a relationship between the EGFR mutation status, the use of EGFR-TKI therapy and post-recurrence survival in patients with recurrent NSCLC [6, 7]. Saisho *et al.* [6] reported EGFR mutations and the use of adjuvant chemotherapy to be prognostic factors. Similarly, Shimada *et al.* [7] reported that EGFR-TKI therapy prolongs post-recurrence survival in surgically resected NSCLC patients. On the other hand, these studies did not mention the details of the correlation between the EGFR mutation status and the use of EGFR-TKI therapy. In the present study, the EGFR mutation-positive patients exhibited significantly better outcomes than the other patients. In addition, similar results were observed in the adenocarcinoma cases. These results suggest that the EGFR mutation status should be identified when recurrence develops after surgery, especially in patients with adenocarcinoma. Our study also demonstrated that EGFR-TKI therapy promotes better outcome among patients with an EGFR mutation-positive status than among those with an EGFR wild or unknown status. Although it remains unclear how the EGFR mutation status impacts the prognosis of NSCLC [22, 23] EGFR mutation-positive patients obtain significant benefits from EGFR-TKI therapy. In this study, the median survival time of the patients with an EGFR mutation-positive status who received EGFR-TKI therapy was 49 months, and the patients exhibited much longer survival times than the patients with an EGFR wild or unknown status and those who did not receive EGFR-TKI therapy. On the other hand, not all